Systematic review and meta analysis of direct vs. indirect angiosomal revascularisation of infrapopliteal arteries.

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What this paper adds

An angiosome is a block of tissue supplied by a specific artery comprising of skin, subcutaneous tissue, fascia, muscle and bone. The foot and ankle comprise six angiosomes, supplied via the tibial vessels. Revascularisation of tibial vessels (via surgical or endovascular means) for localised tissue loss can be performed directly to the affected angiosome (direct revascularisation (DR)), or not (indirect revascularisation (IR)). This systematic review and meta-analysis shows that DR results in improved wound healing and limb salvage rates compared to IR, with no difference in overall mortality or re-intervention rates.

Objectives

The aim of this systematic review was to evaluate outcomes of direct revascularisation (DR) vs. indirect revascularisation (IR) of infrapopliteal arteries to the affected angiosome for critical limb ischemia. Both open and endovascular techniques were included.

Methods

A systematic review of key electronic journal databases was undertaken from inception to September 2013. Studies comparing DR vs. IR in patients with localised tissue loss were included. Meta-analysis was performed for wound healing, limb salvage, mortality and re-intervention rates, with numerous sensitivity analyses. Quality of evidence was assessed using the GRADE system.

Results

13 cohort studies reporting on 1725 individual limbs were included (endovascular revascularisation: 1199 limbs, surgical revascularisation: 450 limbs, both methods: 76 limbs). GRADE quality of evidence was low or very low for all outcomes. DR resulted in improved wound healing rates compared to IR (OR: 0.41, 95 per cent confidence interval (CI) 0.30-0.57, p<0.00001), and improved limb salvage rates (OR: 0.23, 95 per cent CI 0.11-0.48, p<0.00001), although this latter effect was lost on high quality study sensitivity analysis. Wound healing and limb salvage was improved for both open and endovascular intervention. There was no effect on mortality (OR: 0.72, 95 per cent CI 0.45-1.15, p=0.17) or re-intervention rates (OR: 0.44, 95 per cent CI 0.10-1.88, p=0.27).

Conclusion:

DR of the tibial vessels results in improved wound healing and limb salvage rates compared to IR, with no effect on mortality or re-intervention rates.

Introduction

Taylor and Palmer first described the anatomical concept of the angiosome as a block of tissue comprising of the skin, subcutaneous tissue, fascia, muscle and bone, supplied by a specific artery and drained by a specific vein[1,]. Of the 40 angiosomes throughout the body, the foot comprises of six, arising from the posterior tibial artery (three), peroneal artery (two) and anterior tibial artery (one) (figure 1)[2, 3]. Critical limb ischemia with disease affecting the infrapopliteal vessels presents a well-recognised challenge to the vascular surgeon and interventionist[4].

When planning endovascular or open surgical intervention, target vessel selection is typically dependant on the quality of the outflow vessel and its run-off[5, 6]. Recent evidence has suggested that direct revascularisation (DR) of the ischaemic area (i.e. to the angiosome containing the area of tissue loss) resulted in superior outcomes compared to indirect revascularisation IR during endovascular intervention[3, 6-8]. This is the same principle as restoring inline flow during open infrainguinal bypass surgery[5]. However, indirect revascularisation (IR) may be perfectly adequate when sufficient collaterals are present, as angiosomal reperfusion will occur via these collaterals.[6-8] In addition, endovascular IR may be less risky than DR as there is a perception that target vessel loss after DR may result in a complete loss of blood supply to the affected region.

The evidence concerning the use IR and DR is considered equivocal. While open surgical revascularisation is fairly consistent, endovascular practice varies widely. The aim of this systematic review was therefore to evaluate the outcomes of both endovascular and open DR vs. IR of the infrapopliteal vessels.

Methods

Data sources, search strategy and selection criteria

A systematic review was undertaken utilising the Cochrane collaboration specified protocol[9], and reported *as per* the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement for the conduct of meta-analyses of interventional studies[10]. The following sources were searched without date restrictions: PubMed, Medline via OVID, Embase, the Cochrane Library Database and the Current Controlled Trials register. Studies reporting comparisons of DR vs. IR in patients with critical limb ischemia were included. There was no limitation on publication type or language. In the absence of an appropriately specific MeSH term, the free text search term 'angioso*' was used, which captured the following search terms: angiosoma, angiosomal, angiosome, angiosomes, angiosomic, angiosonics, angiosonographic, angiosonography, angiosonoplasty and angiosorus. An extensive search was also conducted using the 'related articles' function in PubMed, of which the results were limited to human research in the English language, with review articles excluded. In addition the European Journal of Vascular and Endovascular Surgery, Journal of Vascular Surgery and British Journal of Surgery websites were searched individually. The last search date was 28th September 2013. Outcome events were captured when two or more papers presented extractable data.

Studies reporting outcomes comparing DR with IR of the infrapopliteal vessels in patients with critical limb ischemia of non-traumatic aetiology were included. Non-English language papers were excluded, as were papers arising, or suspected of arising, from duplicate publications.

Data extraction, outcome measures and assessment of study quality

Data extraction and assessment of methodological quality was performed independently by two authors (DCB and CPT). On cases of disagreement a consensus was reached amongst all authors. Extracted data consisted of: first author, year of study, study type and design (including if retrospective or prospective, single or multiple centres, if consecutive patients were enrolled), number of participants and individual limbs undergoing revascularisation, duration of follow up, modality of revascularisation (endovascular or surgical bypass), target vessel of revascularisation and quality of study. Angiosomes were considered grouped for tibial ('parent') vessel revascularisation (i.e. n=three), and individually for pedal revascularisation (n=six). A number of papers presented propensity matched data due to significant baseline differences between patient groups. Propensity matched data was extracted preferentially. Data were extracted at one year follow up where available, or if not given, at maximal follow up.

Outcome measures were defined as:

1. Wound healing rate - defined as complete epithelialisation of the target lesion with or without adjunct intervention (e.g. debridement, grafting etc).
2. Limb salvage - defined as absence of major amputation (i.e. proximal to the tarsometatarsal joint).
3. Mortality
4. Re-intervention rate

Outcomes were collected and analysed for individual limbs, except for mortality which was analysed for individual patients, when data were available.

Study quality was assessed using the Newcastle-Ottawa (NO) score, which assigns points depending on the quality of patient selection (maximum four points), comparability of the cohort (maximum two points) and outcome assessment (maximum three points)[11]. Studies with a score ≥ six were considered to be of higher quality.

Statistical analysis and evidence rating

Meta-analysis was undertaken in Review Manager version 5.2.6 (RevMan; Nordic Cochrane Centre, Copenhagen, Denmark). Dichotomous data were analysed using odds ratio (OR) as the summary statistic, and reported with 95 per cent confidence intervals (CI). When required, data were extracted from Kaplan Meier curves by the methods described by Parmar[12]. Random-effects model using the Mantel-Haenszel method were used (assuming significant heterogeneity between studies). Heterogeneity was assessed using an I^2 calculation.

Sensitivity analysis was performed when more than two studies were available for inclusion, and for the following subgroups: endovascular treatment alone, surgical bypass alone, larger studies (n<100), those with propensity matched groups, those with a Newcastle Ottawa score of ≥ six and those with follow up given at one year.

Rating of the quality of evidence and strength of recommendation was undertaken using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system, *as per* Cochrane collaboration recommendation[13]. Quality was assessed depending on: risk of bias, indirectness of evidence, heterogeneity, imprecision of results and publication bias. Cohort studies, by definition, have a 'low' quality of evidence prior to further quality assessment. The presence of one or more serious limitations results in a 'very low' grade of evidence. A serious effect on quality of evidence was considered to occur when >50 per cent of included papers evidenced a risk of bias. Inconsistency was defined as an I^2 of >50 per cent. Indirectness was assumed not to occur in this setting. Imprecision was defined as <50 patients in either cohort. A serious effect on quality of evidence was considered to occur when >50 per cent of included papers evidenced a risk of imprecision. Publication bias was assessed using funnel plots for outcomes with more than ten studies[42].

Results

Paper search and selection process

The initial search yielded a total of 1319 results, of which 28 papers were retrieved for full evaluation. Seven conference proceedings were included within this full evaluation. A total of 13 papers (of which two were conference proceedings) fulfilled the inclusion criteria and were included in the subsequent review (figure 2)[14-26]. Excluded papers of note include three duplicate publications[27-29] and one paper where data was non-extractable[30]. All included papers were cohort studies comparing outcomes of direct revascularisation (DR) to the angiosome (or angiosomes) vs. indirect revascularisation (IR). A total of 1725 limbs were available for evaluation.

Study design and baseline characteristics

Study characteristics are given in table 1. Revascularisation was entirely endovascular in seven papers (1199 limbs)[14, 16, 17, 20, 21, 23, 24], via bypass surgery in five papers (450 limbs)[15, 18, 19, 22, 26], and by both methods in one paper (76 limbs)[25]. Detailed breakdown of outcomes for endovascular and bypass revascularisation were not available for the latter paper, which was therefore excluded from relevant sensitivity analyses. Revascularisation policy was specifically mentioned in four papers; preferentially to the angiosome of the target tissue loss in two[14, 16], whilst the other two papers gave no regard to the affected angiosome[15, 26]. Details of the target vessel revascularised were given in five papers[17, 19, 23, 25, 26], although one provided these data prior to propensity matching[23] (see table 2). Patients undergoing DR were more likely to undergo revascularisation to the anterior tibial/dorsalis pedis artery, and less likely to undergo revascularisation to the peroneal artery, compared to the IR group ($p<0.0001$). Propensity matched groups were provided in three papers[15, 17, 23], with equivalent baseline characteristics between groups. For the remaining papers, baseline differences (i.e. patient co-morbidities, disease location/extent, and revascularisation mode) were significantly different in the DR and IR groups in one paper[18], whilst no significant differences were noted in four[19, 21, 25, 26]. Three papers included diabetic patients exclusively[14, 16, 23]. There were six high quality papers (NO score ≥ six)[15-17, 22, 23, 26]. GRADE quality assessment was 'low' or 'very low' for all outcomes (table 3), suggesting caution is taken when drawing conclusions from the following data.

Outcomes

Data regarding wound healing were given in ten papers (1038 limbs)[14-16, 18-20, 22, 23, 25, 26]. Heterogeneity amongst these studies was low (I^2=0 per cent). Meta-analysis showed that DR was associated with a significantly greater wound healing rate compared to IR (OR: 0.41, 95 per cent CI 0.30-0.57, p<0.00001). This effect was maintained in all sensitivity analysis (figure 3, table 4), with a relatively consistent OR (subgroup test for differences: I^2=0 per cent), and low heterogeneity throughout.

Limb salvage rates were presented in 12 papers (1632 limbs)[15-26]. Heterogeneity amongst these studies was high (I^2=77 per cent). Meta-analysis showed that DR was associated with a significantly improved limb salvage rate compared to IR (OR: 0.23, 95 per cent CI 0.11-0.48, p<0.0001). This effect was maintained on sensitivity analysis for endovascular and bypass revascularisation, and for larger studies. However, this significance was lost for studies with propensity matched groups, a NO score of ≥ six, and those giving follow up at one year, although only marginally in the latter two groups (table 4, subgroup test for differences: I^2=39.7 per cent). Heterogeneity varied within the sensitivity analysis from 0 to 88 per cent.

Mortality rates were presented in six papers (719 limbs)[17, 18, 21, 23, 25, 26]. Heterogeneity amongst these studies was relatively low (I^2=25 per cent). Meta-analysis showed that the method of revascularisation had no effect on mortality rates (OR: 0.72, 95 per cent CI 0.45-1.15, p=0.17, figure 4). Similar results were obtained on a variety of sensitivity analysis (table 4, not analysed for bypass revascularisation due to lack of studies). Heterogeneity varied within the sensitivity analysis from 0 to 53 per cent.

Rates of re-intervention were given in two papers (369 limbs)[16, 23]. Heterogeneity amongst these studies was high (I^2=70 per cent). Meta-analysis showed that the method of revascularisation had no effect on re-intervention rates (OR: 0.44, 95 per cent CI 0.10-1.88, p=0.27).

Discussion

This systematic review identified 13 cohort studies reporting on 1725 limbs, comparing the effect of direct and indirect angiosomal revascularisation. Meta-analysis showed that DR resulted in improved wound healing rates compared to IR for both open and endovascular intervention. Limb salvage rates were also improved in the DR group compared to the IR group, although this significance was lost on sensitivity analysis of higher quality studies. DR had no effect on long term mortality or re-intervention rates.

Strengths and weaknesses

This study represents the only systematic review and meta-analysis of DR vs. IR for CLI to date. An extensive search for relevant studies was undertaken, the majority of included papers were recent publications, and numerous sensitivity analyses were performed. There are limitations to this meta-analysis, as all papers reviewed were observational studies and most were retrospective. Less than half of the studies were high quality according to their NO scores[15-17, 22, 23, 26]. Only four papers clearly defined their practice regarding revascularisation[14-16, 26], of which two would preferentially attempt DR over IR leading to selection bias[14, 16]. Propensity matched groups, and therefore higher quality data, were only provided in three studies[15, 17, 23]. Outcomes for wound healing rates were maintained across sensitity analyses, but not for limb salvage. Heterogeneity was high on certain sensitivity analyses. For these reasons, GRADE assessment of quality of evidence was either low or very low.

A further weakness is that no studies were adequately powered randomised trials comparing DR and IR. The only comparative study to date compared a non-angiosomal (from 2001-05) and angiosomal (from 2005-10) revascularisation policy in a single unit[27]. Preferentially revascularising according to the angiosome model (i.e. attempting DR where feasible) resulted in a significant improvement in wound healing and limb salvage, but not in long term survival, consistent with the results of this meta-analysis.

Explaination of findings and implications for practice

The improved outcomes seen with DR compared with IR may be explained by the absence of adequate inter-angiosomal collaterals, typically seen in patients requiring tibial revascularisation [6, 31, 32]. In the only study to date to examine this, Valera *et al.* compared outcomes of DR to IR in patients with and without adequate collatateral vessels as demonstrated on angiography[25]. DR demonstrated superior outcomes to IR in those deemed as having absent collaterals. However when adequate collaterals were present, IR was comparable to DR. The absence of collateral vessles may prove vital in assessing which patients should be agressively targeted for DR. However, due to the pattern of disease, DR is occasionally technically impossible. Kret *et al*. and Rashid *et al.* reported only 62% and 47% of patients had disease eligible for DR[22, 26], whilst Alexandrescu *et al.* achieved DR in 80% of limbs[27]. This difference may reflect selection bias or different patient populations. Extensive tissue loss or infection may preclude surgical access to gain DR even when arteries are suitable for bypass[15]. Whilst it is clear DR is not always a suitable or viable option, this meta-analysis suggests that the angiosome concept should be considered when planning for distal revascularisation, and DR should be utilised preferentially to IR when it is avaliable as a safe option[33].

A significant number of studies employed tibial angioplasty. Whilst long term patency rates for endovascular intervention in the tibial vessels may be low[34], any improvement in arterial supply (albeit temporary) may be sufficient for wound healing[4], especially in patients with significant co-morbidities or deemed unsuitable for surgical bypass[4, 35, 36]. However there remains some debate as to the long term value of tibial angioplasty, with conservative treatment from some centres showing similar long term outcomes[37, 38]. Presuming intervention is useful, this meta-analysis suggests that endovascular DR improves wound healing and limb salvage rates. Importantly, there was no increase in adverse outcomes (mortality or re-intervention rates) with DR. Some units now perform DR and

IR during the same session. There were no comparable data on this technique, but multiple angioplasties result in improved outcomes compared to single lesion angioplasties[39]. Theoretically, a combined DR and IR would overcome any problems with inadequate inter-angiosomal collateralisation[17].

On sensitivity analysis, DR was (non-significantly) less beneficial for bypass surgery compared to endovascular treatment for both wound healing and limb salvage rates. This may reflect the fact that open surgery is still preferentially chosen when the patient is fit or when good outflow vessels are present. Open IR is performed so selectively in the presence of excellent collateralisation, that outcomes would be expected to approach DR. In contrast, IR may be attempted endovascularly with disease deemed unsuitable for bypass. This could result in a greater rate of failed IR, making DR appear better when undertaken endovascularly compared to open.

Conclusion

There is a benefit of DR for localised tissue loss to improve wound healing and limb salvage rates compared to IR, although this is low quality evidence. Overall there was no difference in mortality or reintervention rates with DR compared to IR. This meta-analysis suggestes that the angiosome concept should be considered when planning distal revascularistion and that direct revascularisation should be performed preferentially. While generally accepted for open surgery, this is the first collated evidence to support this during endovascular intervention.

Source of funding

None.

Conflict of interest

None.

FIgure legends

Figure 1. Angiosomes of the foot and ankle. Three main arteries supply the six angiosomes of the foot and ankle. Left: The dorsum of the foot and dorsum side of the toes are supplied by the anterior tibial artery (ATA) and dorsalis pedis artery. Middle: The posterior tibial artery (PTA) is the major supply to the plantar aspect of the foot via three angiosomes comprising of the calcaneal branch to the heel, the medial plantar artery to the medial foot, and the lateral plantar artery to the lateral foot. Right: The lateral border of the ankle and the outside of the heel is supplied by the peroneal artery (PA). Figure reproduced with permision[17].

Figure 2. PRISMA chart detailing the identification process for eligible studies.

Figure 3. DR versus IR: forest plot for wound healing; all papers and sensitivity analyses.

Figure 4. DR versus IR: forest plot for mortality rates.

Tables

Table 1. Demographic data and Newcastle Ottawa score of included studies. * Conference proceedings (abstract). ND = no data. For outcomes: 1. wound healing, 2. limb salvage rates, 3. overall survival, 4. re-do/further procedure, 5. amputation free survival.

Author (year)	Retrospective / prospective	Number of centres	Consecutive patients	Vascular intervention	Propensity matched groups	Follow up (months)	Patients (n)	Limbs (n)	DR (n)	IR (n)	Outcomes	NO score (max 9)
Alexandrescu (2008)	Retrospective	Multiple	ND	Endovascular	No	17.8	ND	102	85	17	1	4
Azuma (2012)	Retrospective	Single	ND	Bypass surgery	Yes	24	ND	96	48	48	1,2	9
Fossaceca (2013)	Retrospective	Single	ND	Endovascular	No	17.5	201	201	167	34	1,2,4	7
Iida (2012)	Retrospective	Multiple	Yes	Endovascular	Yes	18	236	236	118	118	2, 4, 5	8
Kabra (2013)	Prospective	Single	ND	Bypass surgery	No	6	64	64	39	25	1,2,3	4
Kret (2013)	Retrospective	ND	Yes	Bypass surgery	No	ND	97	106	54	52	1,2,3	6
Neville	Retrospective	Single	Yes	Bypass	No	ND	ND	43	22	21	1	4

(2009)				surgery								
Osawa (2013)	Retrospective	Single	ND	Endovascular	No	ND	38	51	29	22	1,2	4
Oshima* (2012)	ND	ND	Yes	Endovascular	No	12	55	60	31	29	2, 3	4
Rashid (2013)	Retrospective	Single	Yes	Bypass surgery	No	12	ND	141	66	75	1,2	7
Soderstrom (2013)	Retrospective	Single	Yes	Endovascular	Yes	12	ND	168	84	84	1	8
Soon* (2012)	Retrospective	ND	ND	Endovascular	No	ND	350	381	197	184	2	4
Valera (2010)	Retrospective	ND	Yes	Both	No	12	70	76	45	31	1,2,3	5

Table 2. Target for revascularisation (either to named artery or branch of) for DR and IR, as given in four papers. A significantly greater number of limbs in the DR group had revascularisation to the AT/DP, and fewer to the peroneal artery, when compared to the IR group (P<0.0001, Chi-squared test). * Totals greater than limb number given in table two due to multiple angioplasties.

Paper	Direct revascularisation			Indirect revascularisation		
	Anterior tibial/dorsalis pedis	Posterior tibial/plantar arteries	Peroneal artery	Anterior tibial/dorsalis pedis	Posterior tibial/plantar arteries	Peroneal artery
Iida*	105	72	46	77	54	54
Kret	27	26	1	15	6	31
Neville	11	6	5	8	8	6
Valera	37	6	2	10	1	20
Total	180 (52%)	110 (32%)	54 (16%)	110 (38%)	69 (24%)	111 (38%)

Table 3. GRADE analysis and assessment of quality of evidence. Risk of bias was assessed for each included paper, and was assumed to be present when a non-consecutive, or non-propensity matched cohort was analysed, or follow up did not reach 12 months.

Outcome	Limbs (studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence
Wound healing	1038 (10)	Serious	No	No	Serious	NA	Very low
Limb salvage	1632 (12)	Serious	Serious	No	Serious	Serious	Very low
Mortality	719 (6)	No	No	No	No	NA	Low
Re-intervention rate	369 (2)	Serious	Serious	No	No	NA	Very low

Table 4. Outcomes for DR and IR, summary of findings. HG – heterogeneity

Sensitivity analysis	No. of studies (total limbs)	DR (n)	IR (n)	HG I^2 (per cent)	HG p value	Odds ratio (95 per cent CI)	Overall effect Z	p value
Wound healing								
All studies	10 (1038)	639	399	0	0.63	0.41 (0.30-0.57)	5.40	<0.00001
Endovascular revascularisation	4 (522)	365	157	0	0.49	0.35 (0.23-0.54)	4.68	<0.00001
Bypass revascularisation	6 (516)	274	242	0	0.61	0.49 (0.30-0.80)	2.88	0.004
Larger studies	5 (718)	456	262	0	0.67	0.43 (0.30-0.62)	4.52	<0.00001
Propensity matched groups	2 (264)	132	132	0	0.87	0.38 (0.21-0.70)	3.09	0.002
NO>5	5 (712)	419	293	0	0.92	0.46 (0.32-0.68)	3.97	<0.0001
One year FU	5 (682)	410	272	0	0.91	0.42 (0.28-0.63)	4.23	<0.0001
Limb salvage								
All studies	12 (1632)	909	723	77	<0.00001	0.23 (0.11-0.48)	3.97	<0.0001
Endovascular revascularisation	6 (1097)	626	471	88	<0.00001	0.18 (0.06-0.56)	2.95	0.003
Bypass revascularisation	5 (459)	238	221	0	0.50	0.42 (0.22-0.80)	2.65	0.008
Larger studies	6 (1233)	686	547	87	<0.00001	0.31 (0.11-0.87)	2.23	0.03
Propensity matched groups	3 (500)	250	250	0	0.50	0.67 (0.40-1.11)	1.56	0.12
NO>5	6 (948)	537	411	87	<0.00001	0.28 (0.07-1.08)	1.85	0.06
One year FU	4 (605)	299	306	16	0.31	0.59 (0.33-1.06)	1.76	0.08
Mortality								
Overall	6 (719)	380	339	25	0.25	0.72 (0.45-1.15)	1.37	0.17
Endovascular revascularisation	3 (464)	233	231	0	0.98	1.02 (0.65-1.58)	0.07	0.95
Larger studies	3 (510)	256	254	53	0.12	0.78 (0.38-1.61)	0.66	0.51
Propensity matched groups	2 (404)	202	202	0	0.91	0.13 (0.64-1.65)	0.12	0.90
NO>5	3 (510)	256	254	53	0.12	0.78 (0.38-1.61)	0.66	0.51
One year FU	4 (558)	278	280	0	0.53	0.89 (0.59-1.35)	0.54	0.59
Re-intervention								
All studies	2 (369)	251	118	70	0.07	0.44 (0.10-1.88)	1.10	0.27

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